1654

In the United States Patent and Trademark Office

Applicant: Lezdey et al

Serial No.: 09/957,012 Examiner: Coe

Filed: 09/20/2001 Art Unit: 1654

For: Oral Methods of Treatment

Box Amendment- Fee
Commissioner for Patents
Washington, DC. 20231

TRANSMITTAL

Dear Sir:

Please find enclosed for filing:

__X__ Post Card

__X__ Attachment from Merck Manual

Date: May 6, 2003

Docket No.: 1434-K

Respectfully submitted,

John Lezdey
Registration No. 22,735
John Lezdey & Associates
4625 East Bay Drive

Suite 302

Clearwater, FL 33764

(727) 539-0633

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

On May 6, 2003 DATE OF DEPOSIT

PRINT OR TYPE NAME OF PERSON SIGNING CERTIFICATE

John Lezdey

SIGNATURE OF PERSON SIGNING CERTIFICATE

John Lezdey 05/06/03

SIGNATURE DATE

#8
DMJ
5-23-03

In the United States Patent and Trademark Office

Applicant:	Lezdey et al		
Serial No.:	09/957,012	Examiner:	Coe
Filed:	09/20/2001	Art Unit:	1654
For:	Oral Methods of Treatment		

Box Amendment-No Fee
Commissioner for Patents
Washington, DC. 20231

Supplemental Response

Submitted is an attachment from the Merck Manual which was inadvertently omitted from the Amendment mailed May 1, 2003.

Respectfully submitted,

John Lezdey
Registration No. 22,735

John Lezdey & Associates
4625 East Bay Drive
Suite 302
Clearwater, FL. 33764
(727) 539-0633

TABLE 105–3. CLASSIFICATION OF SYNOVIAL EFFUSIONS

	Normal	Noninflammatory	Inflammatory	Septic
Gross examination				
Viscosity	High	High	Low	Variable
Color	Colorless	Yellow	Yellow	Variable
Clarity*	Transparent	Transparent	Translucent	Opaque
Routine laboratory examination				
WBC count†	< 200/μL	200–2,000/μL	2,000–100,000/μL	>100,000/μL
PMN %†	< 25	< 25	> 50	> 75
Culture	Negative	Negative	Negative	Often positive

PMN = polymorphonuclear leukocytes.

*Extremely cloudy or opaque effusions can also be produced by crystals, tissue fragments, amyloid, or red blood cells, as well as by leukocytes.

†WBC count and PMN % in septic arthritis will be lower if organism is less virulent or partially treated. Some effusions in SLE and other collagen diseases will be only equivocally inflammatory, with WBC count between 500 and 2000/μL.

Modified from Gatter RA, McCarty DJ: "Synovianalysis." *Rheumatism* 20:2–6, 1964; used with permission.

inflammatory but tend to suggest diseases with less inflammatory mechanisms. Each type of effusion suggests certain joint diseases, as shown in TABLE 105–4.

Microscopic examination of a wet synovial fluid smear for crystals (even a few drops of fluid or washings from a joint can be used for culture or examination of crystals), using polarized light, is essential for definitive diagnosis of gout. By placing an inexpensive polarizer over the light source and another between the specimen and the examiner's eye, crystals with a shiny white birefringence will be visible. Compensated polarized light is provided by inserting a first-order red plate, as in commercially available microscopes. One can also reproduce the effects of a compensator by placing 2 strips of clear adhesive tape on a glass slide and placing this slide over the lower polarizer. Sodium urate crystals then appear strongly birefringent with *negative* elongation; ie, yellow parallel to the axis of slow vibration marked on the compensator (or the long axis of the slide). Calcium pyrophosphate dihydrate **(CPPD)** crystals appear weakly birefringent with *positive* elongation; ie, blue in the direction that urates are yellow. Sodium urate crystals tend to be needle- or rod-shaped; CPPD crystals are rhomboid or rod-shaped. Most crystals of both types are 2 to 15 μ in length. Calcium oxalate crystals seen in some patients with renal failure are bipyramidal and birefringent. Cholesterol, other lipids, recently injected intra-articular corticosteroids, oxalate or other anticoagulants, glass fragments, fibrils from lens paper, starch from gloves, and dirt also appear crystalline or as birefringent objects and may be confused with the crystals. Clumps of apatite crystals are not birefringent with polarized light but appear as shiny, slightly irregular or "coinlike" particles. They can be stained with alizarin red S to confirm that they are calcium-containing.

Other findings in synovial fluid that may yield or suggest a specific diagnosis include LE cells formed in vivo, marrow spicules (due to fracture), specific organisms (identifiable by Gram or acid-fast stain), amyloid fragments (identifiable by Congo-red stain), sickled erythrocytes (due to sickle cell hemoglobinopathies), and iron in large mononuclear synovial cells (identifiable by Prussian-blue stain, and representing hemochromatosis or pigmented villonodular synovitis).

Comparing synovial fluid and serum complement levels may occasionally be helpful in evaluating inflammatory fluids. The synovial fluid complement level tends to be < 30% of the serum complement level in RA but is often higher in gout, Reiter's syndrome, and

TABLE 105–4. DIFFERENTIAL DIAGNOSIS BASED ON SYNOVIAL FLUID CLASSIFICATION (PARTIAL LISTING)

Noninflammatory	Inflammatory	Septic	Hemorrhagic
Osteoarthritis	Rheumatoid disease	Bacterial infections	Trauma with or without fracture
Trauma	Reiter's syndrome		Pigmented villonodular synovitis
Osteochondritis dissecans	Psoriatic arthritis		Neurogenic (neuropathic) arthropathy
Neurogenic (neuropathic) arthropathy	Ankylosing spondylitis		Hemangioma
Sickle cell disease	Ulcerative colitis		Hemophilia
Osteochondromatosis	Regional enteritis		Anticoagulant treatment
Subsiding or early inflammation	Acute crystal synovitis (gout and pseudogout)		Scurvy
Hypertrophic pulmonary osteoarthropathy	Partially treated or less virulent bacterial infections		Thrombocytopenia
Ehlers-Danlos syndrome	Lyme disease		Tumor
Amyloidosis			
Metabolic diseases causing osteoarthritis			
Systemic lupus erythematosus			
Rheumatic fever			
Progressive systemic sclerosis			

Modified from Gatter RA, McCarty DJ: "Synovianalysis." *Rheumatism* 20:2–6, 1964; used with permission.

infectious arthritis. Synovial fluid complement levels will be low (ie, normal) in noninflammatory effusions in which little protein is present. Both serum and synovial fluid complement levels may be low in SLE. **Measurements of rheumatoid factor** in synovial fluid can give misleading false-positive or false-negative results. Extremely low synovial fluid glucose levels may favor the presence of infection.

106. DIFFUSE CONNECTIVE TISSUE DISEASE

RHEUMATOID ARTHRITIS (RA)

(See also JUVENILE RHEUMATOID ARTHRITIS in Ch. 200)

A chronic syndrome characterized by nonspecific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures; generalized manifestations may also be present.

Etiology and Incidence

Etiology is unknown. The immunologic changes (see also AUTOIMMUNE DISORDERS in Ch. 20) may be initiated by multiple factors. About 1% of all populations are affected, women 2 to 3 times more commonly than men. Onset may be at any age, but it most often occurs between the ages of 25 and 50 yr.

Pathology

In chronically affected joints, the normally delicate synovial membrane develops many villous folds and thickens because of increased numbers and size of synovial lining cells and colonization by lymphocytes and plasma cells. The lining cells produce a variety of materials, including collagenase, interleukin-1, and prostaglandins. The colonizing cells, initially perivenular but later forming lymphoid follicles with germinal centers, synthesize

interleukin-2, other kinins, rheumatoid factor **(RF)** and other immunoglobulins. Fibrin deposition, fibrosis, and necrosis also are present. These findings are typical but not diagnostic. Hyperplastic synovial tissue (pannus) may erode cartilage, subchondral bone, articular capsule, and ligaments. Polymorphonuclear leukocytes are not prominent in the synovium but often predominate in the synovial fluid.

The **rheumatoid nodule,** seen in 30 to 40% of patients and usually found subcutaneously at sites subject to trauma, is the most characteristic pathologic lesion. It is a nonspecific necrobiotic granuloma consisting of a central necrotic area surrounded by "palisaded" mononuclear cells with their long axes radiating from the center, all enveloped by lymphocytes and plasma cells. Nodules and **vasculitis** have been found at necropsy in many visceral organs in severe cases of RA but are clinically significant in only a few cases.

Symptoms and Signs

Onset may be abrupt, with simultaneous inflammation in multiple joints, or (more frequently) insidious, with progressive joint involvement. Tenderness in nearly all "active" (inflamed) joints is the most sensitive physical sign. Synovial thickening, the most specific physical finding, eventually occurs in most active joints. Symmetric involvement of small hand joints (especially proximal interphalangeal and metacarpophalangeal), feet (metatarsophalangeal joints), wrists, elbows, and ankles is typical, but initial manifestations may occur in any joint. Stiffness lasting > 30 min on arising in the morning or after prolonged inactivity is common; early afternoon fatigue and malaise also occur. Deformities, particularly flexion contractures, may develop rapidly. Ulnar deviation of the fingers with slippage of the extensor tendons off the metacarpophalangeal joints is typical. The carpal tunnel syndrome can result from wrist synovitis. Ruptured popliteal cysts can mimic deep venous thrombosis.

Subcutaneous rheumatoid nodules, though not usually an early manifestation, can be a major aid in diagnosis. Visceral nodules, vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, lymphadenopathy, Sjögren's syndrome, and episcleritis are other extra-articular manifestations. Fever may be present and is usually low-grade, except in the adult-onset **Still's disease,** a seronegative RA-like polyarthritis with prominent systemic features (see also JUVENILE RHEUMATOID ARTHRITIS in Ch. 200).

Laboratory and X-ray Findings

A normochromic (or slightly hypochromic)-normocytic anemia, typical of other chronic diseases, is found in 80% of cases; the Hb is usually > 10 gm/dL but may rarely be as low as 8 gm/dL. Superimposed iron deficiency or other causes of anemia should be sought if the Hb is < 10 gm/dL. Neutropenia is found in 2% of cases, often with splenomegaly **(Felty's syndrome).** Mild polyclonal hypergammaglobulinemia and thrombocytosis may be present.

The ESR is elevated in 90% of cases. Antibodies to altered γ-globulin, the so-called **rheumatoid factors (RFs),** as detected by agglutination tests (eg, the latex fixation test) that show IgM RF, are found in about 70% of cases. Though RFs are not specific for RA and are found in many diseases (including granulomatous diseases, chronic liver disease, and SBE), a high RF titer provides helpful confirmation when the typical clinical syndrome is present. The **latex** and **bentonite tube dilution tests,** utilizing human IgG adsorbed to particulate carriers such as latex or bentonite, are less specific but more sensitive than the sensitized sheep cell test using rabbit IgG. In most laboratories, a latex fixation tube dilution titer of 1:160 is considered the lowest positive value favoring a diagnosis of RA. A very high RF titer suggests a worse prognosis and is often associated with progressive disease, nodules, vasculitis, and pulmonary involvement. The titer can be influenced by treatment or spontaneous improvement and often falls as inflammatory joint activity decreases.

The **synovial fluid,** abnormal during active joint inflammation, is cloudy and sterile, has reduced viscosity, and usually contains 3000 to 50,000 WBCs/μL. Polymorphonuclear

TABLE 106–1. REVISED CRITERIA FOR CLASSIFICATION OF RHEUMATOID ARTHRITIS (1987)

Any 4 criteria must be present to diagnose rheumatoid arthritis; criteria 1 through 4 must have been present for ≥ 6 wk.

1. Morning stiffness for ≥ 1 h
2. Arthritis of ≥ 3 joint areas
3. Arthritis of hand joints (wrist, metacarpophalangeal or proximal interphalangeal joints)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor, by a method positive in < 5% of normal control subjects
7. Radiographic changes (hand x-ray changes typical of rheumatoid arthritis that must include erosions or unequivocal bony decalcification)

Modified from Arnett FC, Edworthy S, Block DA, et al: "The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis." *Arthritis Rheumatism* 31:315–324, 1988; used with permission.

cells typically predominate, but > ½ of the cells may be lymphocytes and other mononuclear cells. Leukocyte cytoplasmic inclusions may be seen on a wet smear but are also present in other inflammatory effusions. Synovial fluid complement is often < 30% of the serum level. Crystals are absent in pure RA, excluding gout and pseudogout.

Radiologically, only soft tissue swelling is seen in the first months of the disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may be present. The rate of deterioration, both radiologically and clinically, is highly variable.

Diagnosis

The American College of Rheumatology (formerly, the American Rheumatism Association) has proposed new simplified criteria for the diagnosis of RA (see TABLE 106–1) that eliminate the previous terminology of "possible," "probable," "definite," and "classic." While primarily intended as a communication aid for those in clinical research, these criteria can serve as a guide to clinical diagnosis. Almost any other disease that causes arthritis must still be considered as a potential exclusion. Some patients with crystal-induced arthritis can meet the new proposed criteria, so that synovial fluid examination may often be helpful to exclude these. Most exclusions should be considered relative, since diseases causing arthritis occasionally coexist.

When diagnosis is in doubt, subcutaneous nodules should be biopsied to differentiate gouty tophi, amyloid, and other nodules.

RA shares many features of other collagen vascular diseases, particularly SLE, but the latter usually can be distinguished by the characteristic skin lesions on light-exposed areas, temporal-frontal hair loss, oral and nasal mucosal lesions, joint fluid with a WBC count often < 2000/μL (predominantly mononuclear cells), positive antibodies to double-stranded DNA, renal disease, and low serum complement levels. LE cells, positive antinuclear factors, and visceral organ involvement are found in about 5% of otherwise typical RA patients, giving rise to the term **"overlap syndrome."** Some of these cases may represent severe RA; others have associated SLE or other collagen disease. Polyarteritis, progressive systemic sclerosis, and dermato(poly)myositis may have features that resemble RA.

Sarcoidosis, amyloidosis, Whipple's disease, and other systemic diseases may involve joints; biopsy of appropriate tissues often differentiates these conditions. **Acute rheumatic fever** is differentiated by a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin-O **[ASO]** titer). Changing cardiac murmurs, chorea, and erythema marginatum are much less common in adults than in children. Infectious arthritis usually is monoarticular or asymmetric. Diagnosis depends